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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,758	04/24/2001	Olga Bandman	PF-0163-2 DIV	6839

7590 10/03/2002

Legal Department
Incyte Genomics Inc
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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/841,758	Applicant(s) BANDMAN ET AL
	Examiner Christopher H Yaen	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3-12 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I (claims 1,2,13, and 14) in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the search of groups I in addition to groups II, III, IV, VI, and VII would not pose undue burden onto the examiner. This is not found persuasive because the inventions of groups II, III, IV, VI, and VII are drawn to polynucleotide and transformed cell, antibody, a method of producing a polypeptide, a method of screening for an agonist, and a method of screening for an antagoinist, respectively, are all patentable distinct inventions, classified in different classes and subclasses from that of the elected invention. Furthermore, groups II, III, VI, and VII require searches in different databases, which poses additional burden onto examiner.

The requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 1-20 are pending, claims 3-12, 15-20 are withdrawn from consideration as being drawn to non-elected subject matter, and claims 1-2, 13 and 14 are therefore examined on the merits.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-2 and 13-14 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 1-2 and 13-14 are drawn to an amino acid sequence of SEQ ID NO:1, a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, a biologically active fragment of SEQ ID No:1, an immunogenic fragment of SEQ ID No:1, and a composition comprising an amino acid sequence of SEQ ID NO:1 in a pharmaceutically acceptable excipient.

The disclosed utilities for the HSEBP protein comprising the amino acid sequence of SEQ ID NO:1, or naturally-occurring amino acid sequences with at least 96% identity with SEQ ID NO:1 include diagnosis, prevention and treatment of chemically-induced damage, carcinogenesis, and cancer (specification, pp.1, 2, and 25). However, neither the specification nor any art of record teaches what HSEBP is, or what it does do. Furthermore, the specification does not disclose any amino acids which are 96% identical to that of SEQ ID No: 1. They do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for HSEBP, such as the production of and screening of antibodies and antagonists apply to many unrelated polypeptide structure sequences. Therefore, the asserted utilities are not considered "specific" utilities, i.e. they are not specific to HSEBP. Additional disclosed utilities for HSEBP include therapy and diagnosis of conditions and diseases characterized by the expression of HSEBP. The asserted utilities for HSEBP is based on the assertion that HSEBP (SEQ ID NO:1) has chemical and structural homology to selenium-binding proteins (specification, p.3 last line and p.16) and that in particular HSEBP and human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding

protein, share 96%,86%, and 88% identity, respectively (specification pp. 12 lines 30-31). However, it is clear that, although there is a 96%, 86%, and 88% identity between human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein and SEQ ID NO:1, there is a 4%, 14% , and 12% dissimilarity between SEQ ID NO:1 and the sequence of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at

position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 4%, 14%, and 12% dissimilarity to human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, nor would it be expected to be the same as that of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both

molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon

analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Scott et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 4%, 14% and 12% dissimilarity to human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein, nor would it be expected to be the same as that of human fetal heart selenium-binding protein, mouse liver selenium binding protein, and mouse liver acetaminophen-binding protein. Further, even if the polypeptide of SEQ ID NO: 1 are human fetal heart selenium-binding protein, mouse liver selenium binding protein, or mouse liver acetaminophen-binding protein -like proteins, neither the specification nor any art of record teaches what the polypeptide is, what it does. They do not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific and/or well established utility for the reasons set forth, credibility of any utility cannot be assessed.

5. Claims 1-2 and 13-14 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specifc asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

6. Claims 1-2, and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claim 1 and dependent claims thereof, in the recitation of the phrase "an amino acid sequence", because the term can encompass any amino acid sequence from two amino acid sequence to a full-length protein, it metes and bounds can not be fully determined. Clarification is required.

8. Claims 1-2 and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to a naturally occurring

amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, biologically active fragments of SEQ ID No:1 or immunogenic fragments of SEQ ID No:1.

Claims 1-2 and 13-14 are drawn to a naturally occurring amino acid sequence having at least 96% sequence identity to SEQ ID NO:1, biologically active fragments of SEQ ID No:1 or immunogenic fragments of SEQ ID No:1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides, or the polypeptides encoded thereby. Adequate written description requires more than a mere statement that it is part of the invention

and a reference to a potential method of isolating it. The nucleic acid and/or protein itself is/are required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for naturally occurring amino acid sequence having at least 96% identity with SEQ ID NO:1, which reads on allelic variants is provided in the specification on page 13, lines 7-8 , where it is disclosed that the invention encompasses HSEBP variants, at at least about 80%, 90% and 95% amino acid sequence identity with the amino acid sequence of HSEBP. Allelic sequence would be expected to encode polypeptide allelic variants. However, no disclosure, beyond the mere mention of allelic variants, and thus the variant polypeptides encoded thereby, is made in the specification. This is insufficient to support the generic claims as provided by the

Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Yaen whose telephone number is (703) 305-3586. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Christopher Yaen, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Christopher Yaen
Art Unit 1642
September 6, 2002

Brenda Brumback
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